EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327**
THIS DOCUMENT RELATES TO: **Wave 8 Cases**	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

EXPERT REPORT OF OZ HARMANLI, M.D.

ON TVT / TVT-O MIDURETHRAL SLINGS

I. QUALIFICATIONS

I am a Urogynecologist, also known as a Female Pelvic Medicine and Reconstructive surgeon. My current practice location is Yale School of Medicine and Yale New Haven Hospital System in New Haven, Connecticut. I was board certified in Obstetrics and Gynecology in 1997, and Female Pelvic Medicine and Reconstructive Surgery in 2013. I am licensed to practice medicine in Connecticut and Massachusetts.

I am infatuated with learning for my own edification. My intrinsic passion originates from a persistent desire to avoid complacency. Throughout my career, I have been intrigued with innovation but will not adapt it unless its mechanism makes clear sense to me.

Throughout my education, I consistently ranked at the top among my peers locally, regionally, and nationally. I graduated from the most elite medical school in Turkey in 1986. Even though I began my residency training in Obstetrics and Gynecology in Turkey, but I eventually followed my dreams and

came to the United States in 1990. I was so proud when I completed my residency at Temple University School of Medicine in Philadelphia in 1995 as I had always envisioned to pursue an academic career in this country. After completing two residencies; one in my native Turkey, and another one in the USA, I joined the teaching faculty at Temple University as soon as I graduated. I immediately took on leadership roles and became the Associate Residency Program Director. I was very privileged to have one of the nation's most skilled pelvic surgeons at the time, Dr. Marvin H. "Terry" Grody, as my mentor. Under his mentorship, I was able to gain sophisticated surgical skills in the budding field of Urogynecology and Pelvic Reconstructive Surgery. I completed a formal fellowship under Dr. Grody's directorship in 1999.

In 2000, I took over the directorship position from Dr. Grody and continued my busy academic and clinical activities at Temple University until I was recruited to lead the Urogynecology division by Baystate Medical Center of Tufts University School of Medicine in Massachusetts in 2004. I first became a professor of OB/GYN at Tufts University, then at University of Massachusetts (UMASS) after Baystate became an academic center for UMASS Medical School in 2015. In 2017, I transferred to Yale School of Medicine to become the chief of Urogynecology and reconstructive Surgery and professor of OB/GYN, the position I am proudly holding now.

I have authored more than 80 peer-reviewed publications, many international book chapters, and conference presentations. I have been on the editorial board of the Journal of Female Pelvic Medicine and Reconstructive Surgery, the official journal of American Urogynecology Society. I have chaired the Education Committee of Society of Gynecologic Surgeons, (SGS). I have led the vaginal hysterectomy task force for SGS and ACOG and created several teaching modules for American Professors of Gynecology and Obstetrics (APGO)/ Council on Resident Education in Obstetrics and Gynecology (CREOG). I was a member of the systematic review group (SRG) of SGS when I was on the

Research committee of SGS and participated in the publication of systematic reviews including the reviews focusing on midurethral slings and transvaginal mesh procedures for pelvic organ prolapse.

In addition to my career in academics, I have a significant amount of clinical experience. I have performed thousands of gynecologic procedures, most of which have been for urinary incontinence and pelvic organ prolapse. I have been the "last resort" for many of my colleagues when they needed an extra hand, or a "seasoned" opinion for complicated cases. I consider myself an expert in the management of any problem associated with the female genitourinary system except for malignancies. I have developed skills to perform an entire spectrum of complex vaginal, laparoscopic and robotic procedures for non-malignant female pelvic floor disorders.

In the early 1990s, I performed vaginal Kelly-Kennedy plication, Retropubic colposuspension or urethropexy procedures such as Marshall Marchetti Krantz and Burch procedures, and autologous fascial pubovaginal sling procedures for stress urinary incontinence (SUI). I performed some "needle suspension" procedures as well but stopped doing them when the evidence and my personal experience indicated that they did not produce durable outcomes. Among the retropubic procedures, Burch became more widely accepted and eventually was considered the gold standard, however; it was not a very popular procedure from the patients' perspective as it required an incision as large as a one done for cesarean delivery, several days of hospitalization, and many days of post-operative catheterization in about a third of patients'. I had a tough time justifying an open procedure for stress urinary incontinence, which is not life-threatening and subjects the patients to potential serious consequences, including those referenced above. However, I felt obligated to perform numerous Burch procedures as the only minimally invasive option available at the time, as the vaginal Kelly-Kennedy plication was not as effective in the long term.

The TVT was cleared by the FDA in January 1998. TVT is composed of the same Prolene fibers that were approved by the FDA as a New Drug Application (NDA) in 1969. I performed my first TVT midurethral sling procedure in 1999. TVT was a novel, state of the art, minimally invasive approach that was fundamentally different from everything we ever did to treat SUI, including the different mechanism of placing the mesh sling at the midurethra instead of the bladder neck. Unlike Burch colposuspension or autologous fascial sling procedures, TVT could be done through small incisions under local anesthesia and the sling did not have to be anchored. Tension free and midurethral placement concepts made it less likely to cause postoperative voiding difficulty and de novo urge symptoms, something very hard to comprehend at that time. I was fascinated with this revolutionary approach as I was able to treat a non-life-threatening condition with a very minimally invasive method that resulted in equal to or better efficacy than other procedures, fewer complications, quicker operating time, less blood loss, and quicker patient recovery time. The introduction of TVT transformed my practice dramatically. I stopped the routine use of suprapubic catheters, a urinary catheter placed through the pubic skin into the bladder, as voiding difficulty more than a few days was common with previous procedures but far less common with TVT. I have performed a few thousand midurethral sling procedures in the past 20 years. Depending on the availability and some specific characteristics of the patients, I have used almost all of the full-length midurethral slings from a variety of manufacturers including original “bottom-up” method, top-down variation, and the transobturator technique.

I have rarely performed any other procedure such as Burch procedure or rectus fascia sling to treat SUI since I transitioned to midurethral slings. Today, in fellowship programs which train the next-generation of urogynecologists, only a handful of these procedures are performed because of extremely favorable outcomes and very rare complications with midurethral slings have made it unnecessary to consider these more complex procedures.

II. MATERIALS REVIEWED

The purpose of this report is to present my opinion on TVT and TVT-O Midurethral sling procedures. My opinion derives from the following:

1. Exhaustive review of scientific literature
2. Over 20 years of clinical experience
3. Ethicon TVT Instructions for use
4. Professional Education materials made available to pelvic floor surgeons about the TVT devices.
5. TVT Surgeons' Resource Monograph
6. Other documents made available to me and documents that I have reviewed throughout my career
7. Professional society analyses, position statements, systematic reviews, practice guidelines, learning curricula, and training guidelines from organizations including but not limited to AUGS, SUFU, ACOG, AAGL, SGS, IUGA, AUA, NICE, EAU, ACGME, ABOG, and ABU
8. Plaintiffs' expert reports and the materials cited by Plaintiffs' experts.

III. FEES AND EXPERT TESTIMONY

My fees for serving as an expert in this matter are: $400/hour for review, report drafting and meetings and $4,000/day for deposition and trial testimony. I have prepared expert testimony on several cases in the last four years. I have not been deposed during this time.

IV. OPINIONS

a. Stress Urinary Incontinence

Stress urinary incontinence (SUI) is urine loss upon coughing, laughing, sneezing, or physical activity. Depending on the population studied, it may affect 20–40% of all women. SUI differs from urge

urinary incontinence (UUI), which is associated with urine loss upon urge and not related to physical exertion. According to the National Health and Nutrition Examination Survey, 51% of women report urinary incontinence, the majority of whom (49%) experience SUI (Dooley et al).

Annual economic burden of UI is approximately $20 billion when the cost of nursing home admissions, adult diapers, medical and surgical treatments, and time lost from work are all taken into consideration (Hu 2004). Even though urinary incontinence (UI)is not typically life threatening, it significantly impacts the social, psychological, vocational, and relationship aspects of life. Coital urinary incontinence commonly limits sexual activity in a relationship. Women who suffer from SUI tend to be limited in physical and social activities. Older patients in nursing homes with SUI are at greater risk for falls.

SUI is a major problem of the aging and obese women. With the ever-increasing aging population and obesity epidemics, UI burden will predictably continue to grow. An effective treatment for SUI has never been more essential from a public health standpoint. To date, the synthetic midurethral sling like the TVT and TVT-O are the best treatment option available for the index patient with SUI. Midurethral slings are not indicated to treat urgency or urge incontinence.

UI can interfere with a woman's physical health, functional abilities, and emotional well-being, and can substantially reduce quality of life. It can affect their ability to perform in the workplace as well as limit their ability to exercise due to fear of urine loss and the resulting embarrassment. Many women stop exercising with fear of urine loss. They retire early or change career because their work demands long hours of standing and strenuous physical activity. Depriving women from an effective treatment for UI will be a major disservice to women.

b. Alternatives to TVT and TVT-O midurethral slings

An estimated 13.6% of American women will undergo surgical treatment of SUI in their lifetime (Lavelle, OBGYN Clinic NA, 2016). Through the decades, numerous treatment modalities and surgical procedures have been proposed and popularized.

Pelvic floor muscle training, ideally under the supervision of physical therapist has proven to be an effective first line treatment for SUI. Usually surgery can be contemplated when pelvic floor muscle training fails to improve SUI. The vaginal route has always been used more commonly for the treatment of SUI as it offers a less invasive option. However, the most popular vaginal technique prior to the introduction of the TVT was the Kelly-Kennedy plication procedure was not found to be durable in the long term. The search for a better procedure led to the introduction of retropubic colposuspension and urethropexy technique. This procedure was performed through an about 8 cm horizontal incision in the suprapubic area and aimed to place a set of two bilateral sutures between periurethral tissue and a firm anatomic location in that area. When the sutures were anchored to the pubic periosteum as in Marshall Marchetti Krantz technique, occasional development of pubic periostitis occurred and led to the discovery of a safer anchoring point, the Cooper ligaments. This modification of retropubic urethropexy was called Burch procedure after its inventor. The Burch procedure was effective than the Kelly plication, but it was not easy for many surgeons to adopt as the extensive dissection of the retropubic space could be complicated by bleeding, DVT, osteitis pubis, and urinary system injury. This procedure was also quite painful due to a large incision and extensive dissection. Voiding problems were so common that many surgeons would routinely place a suprapubic catheter in these cases. Patients had to stay in the hospital longer and had a longer time to full recovery.

Another concern about Burch retropubic suspension was that it could also increase the risk of an enterocele by changing the vaginal axis and subjecting the cul-de-sac to forces generated in the abdomen with straining. In an effort to prevent it, many times we had to turn this typically extraperitoneal procedure to an intraperitoneal one for enforcement of the posterior aspect of the

pelvic floor and expose the patient to more morbidity associated with peritoneal entry such as bowel complications.

Another technique which also proved to be effective was pubovaginal slings. The goal of this procedure was to make a suburethral bladder neck sling out of a strip of autologous fascia, typically harvested from the thigh fascia lata through a separate incision or from the abdominal rectus fascia via a horizontal suprapubic incision. This procedure was also complicated and prolonged urethral catheterization was common place. In a randomized trial, Bergman et al found that only Burch procedure (82%) remained significantly effective but Kelly plication (37%), and modified Pereyra, a periurethral needle procedure (43%) were not and at 5 years (Bergman, AJOG, 1995). Some other less effective alternatives to TVT and TVT-O midurethral slings are as listed below:

1. Vaginal incontinence pessaries have also been marketed to treat SUI. They work by supporting the urethra and providing a better closure of the urethral continence mechanism during physical exertion. ATLAS trial demonstrated that incontinence pessaries were not more effective than supervised pelvic floor muscle exercises (Richter et al, Obstet Gynecol 2010). Combining these two conservative modalities did not perform better than either one by itself. In addition, pessaries need fitting, maintenance, and cleaning. They also may present several adverse effects such as discharge, bleeding, and vaginal irritation and erosion.

2. Periurethral bulking agents are typically less effective for SUI, do not produce a long-lasting effect, require repeat injections, and may be advised only when a midurethral sling cannot be done due to medical co-morbidities. They are sometimes used as a “touch-up” when midurethral sling placement does result in adequate improvement.

3. Laparoscopic Burch procedure, though minimally invasive, is not a straightforward approach. It requires skills which may take a longer time to acquire. It was shown to be as effective as TVT but went out of favor because TVT demonstrated superior benefits regarding safety and reproducibility.

c. TVT Midurethral slings

Because of these relatively complicated options, surgical treatment of SUI was not an easy decision for either the surgeon or the patient. Many patients would try non-surgical methods with no or limited improvement. In an effort to simplify and reduce the morbidity associated with pubovaginal sling procedures, non-autologous material such as cadaveric fascia were introduced, which ultimately many surgeons stopped performing because of higher failure/recurrence rates. That was when the idea of synthetic or biologic graft materials was reborn. The surgical landscape changed dramatically with the introduction of the first minimally invasive midurethral sling, Tension free vaginal tape (TVT), which occurred after years of extensive research by Petros and Ulmsten (Petros and Ulmsten 1995 and 1996). TVT changed the entire paradigm for the surgical treatment of SUI: Even though it was also a suburethral sling, it was intentionally placed at the midurethra with no tension and was not anchored. It utilized Prolene (polypropylene) mesh from Ethicon, which was very commonly used as a permanent suture material in many surgical fields as well as Prolene hernia mesh which had been used to repair hernias since the 1970s. Ulmsten evaluated a variety of meshes but found the best results with Ethicon's Prolene.

TVT is versatile as it is suitable for a variety of patients with SUI, which is not the case for Burch procedure. SUI is typically caused by impaired urethral support but there is a subset of patients with SUI who have intrinsic sphincteric deficiency, a condition Burch procedure would not be able to treat. In those cases, the pubovaginal sling was the most effective approach. This procedure would also require an at about 6-cm incision and harvesting of autologous fascia from the abdominal rectus muscles or the thigh.

TVT as the original midurethral sling procedure presented an option which could be effective regardless of the underlying cause of SUI. This alone was convincing enough for most of pelvic surgeons to switch to this innovative technique.

TVT is effective in women with Mixed urinary incontinence (MUI). MUI, one of the most challenging conditions for urogynecologists, is a type of urinary incontinence when a patient has not only SUI but also urge urinary incontinence (UUI). Every time I see a new patient, I hope she has pure SUI because I know I can cure her problem with midurethral sling placement. Unfortunately, we do not have a treatment modality for overactive bladder (OAB)/urge urinary incontinence (UUI), which produces cure rates comparable to that of midurethral slings for SUI. Today there is overwhelming evidence which indicates that full length midurethral slings whether retropubic such as TVT, or transobturator as in a TVT-O, are not only effective improving SUI but also OAB symptoms in women with mixed urinary incontinence (MUI). This effectiveness is in the range of 50-70%, not much different from the effectiveness of medications and modalities approved or cleared by FDA for the treatment of OAB and UUI (Jain et al, IUJ 2011). In fact, there is an ongoing NIH funded randomized trial, namely ESTEEM, which randomizes women with MUI to either midurethral sling alone or to midurethral sling with behavioral modification (Sung et al, IUJ 2016). This study design confirms that scholars and researchers who designed the study agreed on the fact that midurethral sling is the treatment of choice for MUI but would like to evaluate if it should be performed in combination with behavioral modification or not.

The TVT and its clones have essentially replaced all other treatment options worldwide. Many practice pattern surveys have confirmed the dominance of retropubic and transobturator midurethral slings. To suggest that the Burch or autologous fascial sling is currently the dominant procedure or gold standard for treating SUI is completely unfounded and disingenuous. TVT has become the gold standard in the treatment of SUI. Because it is safe, effective, uncomplicated and well tolerated, it is now offered

as a first line treatment. Describing the TVT as safe does not mean it is without complications, as the potential risks of any pelvic floor surgery are unavoidable and there is no risk-free procedure. The utility, desirability, and benefits of TVT and TVT-O significantly outweigh the risks. In a well-designed randomized trial by Labrie et al, women were randomly allocated to either midurethral slings or supervised pelvic floor physical therapy (Labrie et al, NEJM 2013). Subjective improvement was noted in about 90% of the patients who had a midurethral sling when only about 30% of women who underwent pelvic floor physical therapy had similar improvement. Half of the women who were originally assigned to pelvic floor physical therapy chose to have a midurethral sling, which also was successful in 90% of the patients.

Since the early 2000s, a network of academic institutions funded by the National Institute of Health (NIH) has been conducting a series of seminal randomized trials to identify best treatment options for women with urinary incontinence and pelvic organ prolapse. The first one of them was CARE trial which aimed to evaluate the role of prophylactic incontinence procedures at the time of apical suspension with abdominal sacrocolpopexy. Because it is also an abdominal approach, the Burch procedure was designated exclusively as the incontinence procedure for this trial. Even though the results of CARE trial made a key impact on our current management, that study was criticized for not using TVT because most surgeons had switched almost exclusively to TVT for treatment for SUI by the time CARE trial was published in 2006 (CARE et al, NEJM 2006). Following the CARE trial, the NIH-funded research network decided to allow only TVT for all the following randomized trials such as OPUS and OPTIMAL studies. (Wei et al NEJM 2012, Barber JAMA 2014; Jelovsek 2018). This group evaluated Ethicon's TVT compared to Ethicon's TVT-O and the Monarc transobturator midurethral sling in the TOMUS (Trial of MidUrethral Slings) randomized controlled trial which now has 5-year follow-up. (Kenton 2015, Thomas 2015, Wai 2013, Albo 2012). Similarly, the same group evaluated the Burch

colposuspension compared to the autologous fascial sling in the SISTEr (The Stress Incontinence Surgical Treatment Efficacy Trial).

Today, the majority of abdominal sacrocolpopexy procedures to treat pelvic organ prolapse are performed laparoscopically or robotically. Even though the laparoscopic Burch procedure has been described and was found to be effective, most pelvic surgeons choose to perform a TVT for SUI when they need to treat SUI at the time of a sacrocolpopexy. The dominance of the TVT compared to the Burch was recently demonstrated in a study from the Mayo Clinic finding better cure rates with TVT at 2-year follow-up. (Trabuco 2018; Fusco 2017 Systematic Review; Cox 2013 Review).

There is no procedure which does not have a learning curve. The Burch procedure in beginners' hands may be a very high-risk choice. The Burch and autologous fascial sling procedures are rarely taught in Ob/Gyn residencies. (Walters 2012). I can attest to this as I have spent most of my career training residents and fellows. The primary surgical treatment for SUI that is taught and performed today is the synthetic midurethral sling. Mesh has been used in human body for decades, first for hernia repair. Mesh has been used in female incontinence procedures also for decades. The complications associated with mesh, such as erosion, exposure, or infection have been discussed in the literature for many years and are basic risks that pelvic floor surgeons utilizing mesh are expected to know. Mesh for TVT was so effective that so many similar products were developed but TVT remained as the standard midurethral sling in multi-center studies conducted by an academic network funded by NIH and hundreds of other clinical studies and systematic reviews evaluating TVT and TVT-O. There is unambiguous evidence that the risks of complications for incontinence surgery are usually less severe than for more extensive repairs to treat pelvic organ prolapse. Similarly, the complications, such as mesh exposure are different for midurethral sling procedures such as TVT and TVT-O compared to transvaginal mesh placement for pelvic organ prolapse (Ridgeway et al. The use of synthetic **mesh** in pelvic reconstructive surgery. Clin Obstet Gynecol. 2008 Mar;51(1):136-52). This is in part due to the

surface area as prolapse repairs require a much greater surface area to provide the necessary pelvic floor support, whereas the midurethral slings are only 1cm wide and provide tension-free support under the midurethra. When the FDA issued the 2008 Public Health Notification it mistakenly grouped together all transvaginal meshes for prolapse and incontinence without differentiating as it later did when the FDA released a 2011 Public Health Notification specific to transvaginal mesh for prolapse repairs followed by a 2013 Considerations for mesh used for SUI. When the data was separately analyzed by FDA through a systematic review of the medical literature and review of the MAUDE database, it was clear that midurethral slings such as TVT and TVT-O posed a lower risk compared to the transvaginal mesh procedures for pelvic organ prolapse (FDA 2013). As a result, FDA decided to keep midurethral slings such as TVT and TVT-O in Class II (lower risk) products, which is true as of the writing of my report in 2018, whereas the FDA up-classified all transvaginal mesh devices for pelvic organ prolapse to Class II (higher risk category).

Midurethral sling procedures primarily TVT is the most studied procedure in gynecologic practice. We have long term data up to 17 years (Nilsson 2013; Braga 2018; Bakas 2018).

Wound problems and urinary tract infections (UTI) are less common with TVT. In SISTEr trial which compared Burch and rectus fascia sling procedures showed about 25% wound infection (Albo et al, SISTEr Trial NEJM 2007). According to SISTEr trial, the rate of UTI was 32% and 48%, with the Burch and rectus fascia sling procedures, respectively in the 2 years (Albo 2007) whereas UTI incidence was 17.4% for TVT in the TOMUS trial. (Albo 2012). Our group attempted the first randomized trial of antibiotic prophylaxis for midurethral sling procedures but the study was stopped prematurely as there was no statistically significant difference between the antibiotic and placebo groups, respectively, with respect to wound infections [1 (3.3%) and 0 (0%)], mesh exposure [0 (0%) and 1(3.5%)], and bacteriuria [3 (10%) and 1 (3.5%)] (Harmanli et al, IUJ 2011) 201. We noted that the infection risk is so low that for us to finish the study, we would need almost two thousand patients to achieve adequate power. After

reviewing of the results of this trial and the literature, we decided that stop using preoperative antibiotics for midurethral slings. We then reported our outcomes on 174 women who did not receive preoperative antibiotics for midurethral sling procedure. There were no wound infections, 2 (1.4%) vaginal mesh exposures and 12 (8%) cases of bacteriuria. These numbers clearly indicate that mesh use does not seem to increase infectious complications even when antibiotic prophylaxis is not given (Harmanli et al, IUJ 2012).

d. Instructions for Use (IFU)

The IFUs for TVT and TVT-O are detailed and cover all the requirements set forth by the Code of Federal Regulations (21 CFR 801.109(c)). The IFUs do not exclude any risks specific or unique to the device, as the only unique risk of mesh erosion is described in the IFU. Residents, fellows, and certainly Board-certified pelvic floor surgeons, are expected to know that there are general risks associated with any surgical procedure including but not limited to pain, dyspareunia, infection, UTI, fistula, wound healing problems, erosion/exposure of suture or mesh, failure of the procedure to work, the need to perform another procedure to treat a complication or recurrence, urinary retention or obstruction, voiding dysfunction, perforation of the bladder, bowel, or other structure, bleeding, etc. The most common risks are bleeding, infections, and injury to the surrounding structures. All surgeons must make themselves familiar with the relevant anatomy, the basic principles of surgical technique, the clinical outcomes published in the medical literature, how to counsel patients about the risks and benefits, and how to identify and manage complications. The fact that a procedure utilizes a medical device does not eliminate the responsibility and accountability of the surgeon using it. There was never an IFU to rely on when surgeons performed procedures such as Burch colposuspension or autologous fascial slings, yet they share the same potential risks as midurethral slings. As expected, they used their skills, experience, common knowledge and clinical judgement for those cases. It is not expected in the medical community that surgeons place much, if any, reliance on a manufacturer's Instructions for Use. A survey conducted

by Faber (2017) helps demonstrate the stark contrast of how surgeons don't read or rely on the IFU in clinical practice compared to the importance that is placed on the IFU in this litigation. Pelvic floor surgeons are expected to be familiar with the complications of pelvic floor surgery, and that includes the risks of introducing a permanent suture or mesh. The risks of pelvic floor surgery are commonly known to surgeons regardless of what is contained in the IFU. Learning curricula and guidelines from AUGS, IUGA, ACGME, ABOG, and ABU, as well as my experience instructing residents and fellows and discussions with colleagues at conferences, and my review of the medical literature provide the basis for my opinions.

It is inherent in any type of surgery that there may be some inflammatory process and tendency for scar formation, which cannot always be predictable. Naturally these can lead to dyspareunia and vaginal contractions. There is abundant literature reporting on these risks and outcomes for all vaginal surgeries for decades (Williams TJ, TeLinde RW. The sling operation for urinary incontinence using Mersilene ribbon. Obstet Gynecol. 1962 Feb;19:241-5; Morgan JE. A sling operation using Marlex polypropylene mesh for treatment of recurrent stress incontinence. Am J Obstet Gynecol. 1970 Feb 1;106(3):369-77; Stanton SL. Stress incontinence: why and how operations work. Clin Obstet Gynaecol. 1985 Jun;12(2):369-77; Sweat SD, et al. Polypropylene mesh tape for stress urinary incontinence: complications of urethral erosion and outlet obstruction. J Urol. 2002 Jul;168(1):144-6; Vassallo BJ, Urethral erosion of a tension-free vaginal tape. Obstet Gynecol. 2003 May;101(5 Pt 2):1055-8; Horbach NS, et al. A suburethral sling procedure with polytetrafluoroethylene for the treatment of genuine stress incontinence in patients with low urethral closure pressure. Obstet Gynecol. 1988 Apr;71(4):648-52; Iglesia CB, et al. The use of mesh in gynecologic surgery. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(2):105-15; Tamussino KF, Austrian Urogynecology Working Group.. Tension-free vaginal tape operation: results of the Austrian registry. Obstet Gynecol. 2001 Nov;98(5 Pt 1):732-6; Tamussino K, Austrian Urogynecology Working Group. Transobturator tapes for stress urinary incontinence: Results of

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I have been using TVT for almost 20 years and have used both mechanically cut and laser cur TVT and TVT-O. I can attest to the fact that I have not noticed any clinical difference between mechanically cut versus laser cut mesh with respect to effectiveness or safety in my clinical practice or in the medical literature. There is no clinical data to support and difference, and in fact, recent studies analyzing this issue have confirmed the lack of any clinical significance. (Rusavy 2017; Thubert 2016).

There is a consensus today shared by all professional societies that both retropubic and transobturator mesh midurethral slings are “the gold standard”. Many systematic reviews and meta-analyses of pooled data as well as the statements coming from all professional organizations agree that TVT is the most studied midurethral sling. Compared to other surgical options, midurethral slings provide the best and longest success with the most favorable safety/complication profile. . (2018 Position Statement from AUGS, SUFU, IUGA, ACOG, SGS, AAGL, NAFC; 2017 AUA, SUFU Guideline for Surgical Treatment of SUI; 2015 ACOG Practice Bulletin; 2015 EAU Guidelines; 2014 IUGA Position

Statement; 2014 AUGS FAQs by Providers and Patients; NICE 2013 Guidelines; 2013 AUA Position Statement; 2013 FDA Statement on Midurethral Slings; 2015 Ford Cochrane Review, 2014 Schimpf SGS Systematic Review, 2015 Tommaselli Meta-Analysis of Long-Term TVT and TVT-O Studies, 2011 and 2009 Ogah Cochrane Reviews; , 2017 Fusco Meta-Analysis *update from Novara 2008/2010; 2009/2012 AUA Guidelines Appendix – Complications from Systematic Review' 2013 Cox Review of Meta-Analyses).

The most widely adopted and relied upon position statement was issued by AUGS and SUFU from 2014, which was then reaffirmed and endorsed by other major organizations such as ACOG, AAGL, and SGS before adding the endorsement of IUGA and a description of the European Union's SCENIHR 2015 Report in the updated 2018 position statement. I agree with the position statement that:

1. Polypropylene is safe and effective as a surgical implant. It has been used in almost all surgical fields for decades as a suture material, part of some other surgical implant or as a knitted material as in mesh. Polypropylene mesh has been the most commonly used material for hernia repairs. It was because of its successful use for hernias which made it the most appropriate choice for transvaginal mesh application. The data on safety and effectiveness of mesh used for midurethral slings is also up to 20 years.

2. Midurethral slings made of monofilament polypropylene is the most extensively studied anti-incontinence procedure in history. Randomized clinical trials (RCTs) are regarded to generate the highest quality evidence. There have been more RCTs on this procedure than almost any procedure in the disciplines of urology and gynecology.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of stress urinary incontinence. They are highly effective, less painful, cost less, lead to faster return to normal activities.

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

This position statement clearly concluded that this procedure had improved lives of millions of women and revolutionized the surgical treatment of stress urinary incontinence.

One of the most recent and robust systematic reviews evaluating midurethral slings was conducted by Ford et al for the Cochrane Database in 2015. They selected 81 trials (most of which involved Ethicon's TVT or TVT-O) that included 12,113 women, some long term. The short term subjective cure of TVT was 71- 97%. It maintained its effectiveness in the long term as well. The overall rate of vaginal tape erosion/exposure/extrusion was 2%. The need for a repeat incontinence procedure was the lowest for TVT. This systematic review by Ford et al showed that retropubic bottom-to-top route as in TVT was more effective than top-to-bottom route for subjective cure. It caused significantly less voiding dysfunction, fewer bladder injuries, and vaginal tape erosions. Authors of this review concluded that "Mid-urethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI. However, a bottom-to-top route was more effective than top-to-bottom route for retropubic tapes." The TVT is a "bottom-to-top" retropubic midurethral sling and the TVT-O is an "inside-out" transobturator midurethral sling.

There is ample long-term data on TVT from a variety of populations and many different countries. They all indicate that TVT continues to prevent SUI and very rarely led to complications including mesh revision or removal. Most women remained very satisfied and stated that they would recommend the procedure to their loved ones (2015 Welk 10-year cumulative revision rate of 3.29, 2013 Jonsson-Funk 9 year sling revision/removal rate of 3.7%, 2016 Unger reported a 3.7% revision rate with most revisions occurring at 7.8 months after the implant; 2012 Nguyen Kaiser Permanente).

The primary risk factors for mesh erosion/exposure is surgeon's experience, skills, technique and tensioning. Host factors which may also affect mesh exposure include vaginal atrophy, smoking, diabetes, obesity, prior or concomitant surgeries, and wound healing issues at the incision line. (Kokanali 2014). The IFU warns the patients on complications that are specific to the device and does not need to list the commonly known risks of any pelvic floor procedure. Most mesh exposures occur at the incision line due to wound complications and occur at a frequency of approximately 2% (FDA 2013; Ford 2015; Schimpf 2014). Exposed mesh does not always require another procedure. Local estrogen is often helpful. (AUGS/ACOG 2017 Practice Bulletin on Managing Graft Complications). When a procedure is needed, it is almost always simple and effective.

e. Plaintiffs' Alleged Safer Alternative Designs

Native tissue and suture repairs are not held to the standards which TVT sling has been to because they are not medical devices. This should not be interpreted as though they are safer alternative designs to TVT.

TVT is the most effective and least complicated sling according to all systematic reviews and position statements of professional organizations. According to manufacturer documents, the idea for utilizing a lighter-weight, larger pore, partially absorbable mesh was vetted among pelvic surgeons but was not seen as necessary as there was consensus about safety and reliability of the current mesh composition. Furthermore, mesh exposure was not eliminated when a lighter mesh was used in a small study using a patch of hand-fashioned mesh that is not similar to a midurethral sling. (Okulu 2013).

Erosion and exposure are unavoidable risks for any permanent material including any mesh product, prostheses, and sutures. No currently available mesh compositions can eliminate or significantly reduce complications that are inherent to implantation of permanent foreign material. For example, more than 15% of patients who underwent a sacrospinous ligament fixation or uterosacral

ligament suspension procedure in the OPTIMAL trial experienced a suture erosion or exposure, whereas around only 1% of the 99% of patients who received a concomitant TVT experienced a mesh erosion/exposure. (Barber 2014; Jelovsek 2018 – supplemental tables; Jelovsek JE, et al.; Effect of Uterosacral Ligament Suspension vs Sacrospinous Ligament Fixation With or Without Perioperative Behavioral Therapy for Pelvic Organ Vaginal Prolapse on Surgical Outcomes and Prolapse Symptoms at 5 Years in the OPTIMAL Randomized Clinical Trial. JAMA. 2018 Apr 17;319(15):1554-1565. PubMed PMID: 29677302). Shapiro (2017) recently published a study describing late suture exposures after Burch procedures.

Many other surgical fields place implants of medical devices for orthopedic, urologic, neurologic or cardiac indications, some of which have a less favorable safety and efficacy profile than that of TVT. Surprisingly, they have not been exposed to the level of scrutiny that TVT slings have received.

The systematic review of TVT and other midurethral slings for the entire post TVT era from 1996 to 2011 undertaken by the FDA before the release of 2011 warning concluded that full-length midurethral slings such as TVT were safe and effective in studies with 1-year follow-up with only 2% mesh exposure rate. The FDA considered described mesh exposure as the only unique complication of midurethral slings compared to traditional procedures.

f. Degradation, carcinogenesis

Even though some data exist suggesting a theoretical risk of carcinogenesis in animal models, I have not been able to identify any clinical evidence to support this association in humans. In rat and mouse models, tumors such as sarcoma and fibrous histiocytoma developed only when solid sheets of polypropylene without pores were used (Ostergard IUJ 2014). The mesh used in TVT or TVT-O is macroporous and are not solid sheets. In its 2000 statement, the International Agency for Research on Cancer reported that there was no evidence associating synthetic implants with carcinogenesis in humans (McGregor et al, Eur J Cancer 2000. There have been several population-based studies which

also did not find any association between midurethral polypropylene sling surgery for SUI and an increased cancer risk later in life (Chughtai J Urol. 2017, Altman et al, Obstet Gynecol 2018). There are also substantial data that demonstrates no carcinogenetic effect of mesh implantation (Moalli P., Nager C. Int Urogyn J 2014; King A, Goldman H. Curr Urol Rep 2014; Linder BJ. Int Urogyn J 2016; AUGS/SUFU FAQs for Providers 2014).

Inflammation and reaction to the foreign material are expected consequences of wound healing and should not be considered complications. The connective tissue ingrowth promoted by inflammation is considered necessary for the sling to function almost as an artificial ligament. Falconer et al demonstrated that tissue ingrowth with TVT is excellent (Int Urogyn J 2001). The polypropylene mesh explants were characterized by the greatest number of infiltrating fibroblasts, a favorable histologic finding that confirms healthy tissue ingrowth (Woodruff, 2008).

TVT mesh partially removed from women for obstructive symptoms did not reveal any evidence of graft degradation. To my knowledge, there have not been any report claiming mesh rejections after TVT operations. Nor there has been any statement form any professional organization associating theoretical degradation with any clinically significant event. The clinical data from millions of polypropylene midurethral slings implantations in over 20 years with favorable outcomes result in about 2% mesh related complications make animal research and laboratory testing irrelevant. Animal data is much lower on the Oxford levels of evidence and is far less important or clinically relevant when significant clinical data is available as is the case with TVT and TVT-O. Therefore, the position that TVT IFU must include a warning about the risk and consequences of degradation does not hold any merit. Thus, it is my opinion that degradation and inflammation, whether it exists or not, is not clinically significant. Thames (2017) confirmed the lack of in vivo degradation after properly cleaning and analyzing explanted TVT meshes. Similar findings were reported by (Heinz 1948; de Tayrac 2011; Woodruff 2008; AUGS 2014 FAQs).

A prudent surgeon would be expected to know about the potential risks of pelvic floor surgery and is expected to make his or her patients aware of the natural history of the disease condition, alternatives, and all the risks and benefits of the procedure. No procedure is without risk and TVT is not exempt from that fact. Bleeding, infection, hematoma formation, pain, scarring, dyspareunia, failure, wound healing problems, visceral injury, and many other complications are well-known risks of any procedure which requires sharp instrumentation and tissue dissection. Vast peer-reviewed clinical literature revealed that the risk of any infection is lower for TVT slings than any of its predecessors including Burch and the autologous fascia sling. (Schimpf, 2014). My opinion is that product IFUs for TVT and TVT-O clearly describe the risks associated with the device and appropriately omit the well-known risks that can occur with any pelvic floor surgery with or without mesh.

V. CONCLUSION

SUI is a very common medical problem which interferes with all aspects of life. Even though it is not life-threatening, SUI limits one's ability to engage socially and professionally. The increased prevalence of treating SUI is directly linked to growing aging population, the obesity epidemic, the revolution of TVT and the popularization of the midurethral sling which has increased access to many women who previously elected to live with the burdens of SUI rather than undergoing an invasive Burch or autologous fascial sling procedure, and the increased emphasis and research in the field of female pelvic medicine and reconstructive surgery. Midurethral slings like TVT and TVT-O are the first-line treatment option and current gold standard for treating SUI because they provide the best-studied, most predictable and proven long-term benefit-risk profile with high cure rates and low complications. It would be a travesty if surgeons resorted back to Burch or Autologous fascial slings as primary treatment options. Among numerous surgical procedures proposed to treat SUI, only Burch retropubic urethropexy and autologous fascia slings have been able to improve SUI, however these procedures were harder to do proficiently, required large incisions, resulted in long term voiding problems, required

longer patient recovery times and hospital stays, and have not been subjected to such extensive study and evaluation in many robust clinical trials, systematic reviews, and long-term studies like TVT and TVT-O. (Committee on Practice Bulletins—Gynecology and the American Urogynecologic Society. ACOG Practice Bulletin No. 155: Urinary Incontinence in Women. Obstet Gynecol. 2015 Nov;126(5):e66-81; Tan PF, et al. Effectiveness and complication rates of tension-free vaginal tape, transobturator tape, and tension-free vaginal tape-obturator in the treatment of female stress urinary incontinence in a medium- to long-term follow up. Meta-analysis of randomized controlled trials. Saudi Med J. 2014 Jan;35(1):20-32. Laurikainen E, et al. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. Eur Urol. 2014 Jun;65(6):1109-14; Petros PE, An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl. 1990;153:7-31; Ulmsten U, Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol. 1995 Mar;29(1):75-82; Ulmsten U, An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996;7(2):81-5; discussion 85-6; Falconer C, Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S19-23; Nilsson CG, Long-term results of the tension-free vaginal tape (TVT) procedure for surgical treatment of female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S5-8; Petros P. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. Int Urogynecol J. 2015 Apr;26(4):471-6; IUGA Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence. 2014 July 21; de Leval J. Novel surgical technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out. Eur Urol. 2003 Dec;44(6):724-30. de Leval J, Waltregny D. New surgical technique for treatment of stress urinary incontinence TVT-Obturator: new developments and results. Surg Technol Int. 2005;14:212-21. Bonnet P, Transobturator vaginal tape inside out for the

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Mesh had already been used in human body for many decades primarily for hernia surgery but also for urinary incontinence and pelvic organ prolapse before TVT was introduced. Mesh use never became popular until TVT was developed after years of fundamental, conceptual and laboratory work. The introduction of TVT was revolutionary and a “game-changer” for surgeons and patients. The impact of TVT on SUI treatment is comparable with that of ultrasound on prenatal care and in vitro fertilization on fertility. The introduction of TVT was the definition of “disruptive technology” as it changed the landscape for the treatment of SUI shortly after it was introduced and after the initial results from the landmark Ward-Hilton trial in 2002. Finally, TVT allowed surgeons to offer patients a minimally invasive procedure which not only offered very high success rate but also reduced the morbidity, which used to be a major deterrent for the older surgical procedures for SUI. TVT was immediately embraced by pelvic surgeons around the world and hundreds of studies have confirmed the excellent results reported by Ulmsten. Millions of women are able to enjoy an active life without the embarrassment of leaking urine, or the burden of wearing pads and changing clothes, as a result of TVT and all the other midurethral slings which mimicked its revolutionary paradigm.

TVT was introduced only after years of research including animal studies and clinical studies, including a multi-center trial to ensure that less-experienced surgeons could achieve the same outcomes as the inventor. The research supporting TVT before its launch far exceeded the standard of its era. The manufacturer followed all the guidelines when it prepared TVT for the market. Its IFU included all the risks which can be specifically attributed to the design and structure of the product.

The TVT and TVT-O have more prospective and long-term data than any other procedure that I know in genitourinary medicine. It is my observation that there probably has not been any other medical device in any field of medicine which was studied more than TVT. There have been well over 50 randomized trials, 2000 publications, and numerous systematic reviews focusing on TVT and TVT-O. It is the consensus of all gynecologic, urologic and urogynecologic organizations that TVT is the gold standard. TVT has revolutionized SUI treatment. It is versatile and fits for almost women of all background and demographics. TVT results in immediate success in about 80-90% of the patients. This life-changing procedure allows patients to resume normal activities within days after the procedure. It has reduced morbidity associated with the older SUI procedures and made it more acceptable to women. Voiding problems are rare and usually resolve within days. Mesh related problems and reoperation for mesh issues are within 2% across the studies and are usually easily treated.

There is up to 17 year-long data on TVT which clearly shows that most patients are very satisfied with the procedure. Prospective good-quality data indicates that pain and dyspareunia improves after TVT. The theories which purport that it may be degraded, thereby rejected or lead to cancer after its implantation has never been substantiated with credible clinical data.

For any surgical procedure, one of the most important variables is the surgeon's skills and judgement, however; patients with some risk factors may experience more problems with any procedure. Most problems such as bleeding, infection, wound dehiscence, organ injury, and chronic discomfort from scarring, which are commonly attributed to TVT, are not specific to this procedure. Since the introduction of the product, the manufacturer has made all reasonable efforts to educate, train, and warn the practitioners.

Today TVT is mainstay of SUI treatment. It is the most efficacious procedure for SUI and has the best safety profile than any other sling. Its complications are very rare and very treatable. I cannot

envision managing SUI without TVT. Millions of women would have been desperate and helpless had TVT not been invented. Going forward, depriving women from one of the most impactful procedures in women's health will be an unfortunate disservice to betterment of quality of life of women of the world.

Signed:

Oz Harmanli, M.D.

August 9, 2018